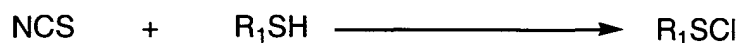


CLAIMS

We claim:

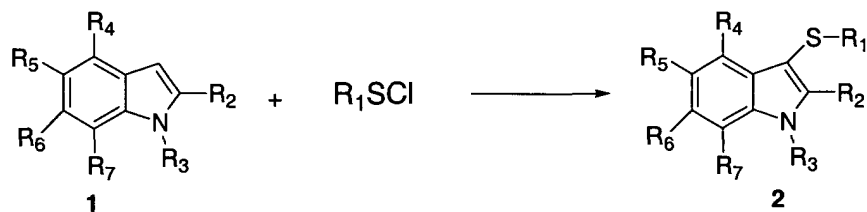
5 1. A one-step method for the sulfenylation of 2-carboxyindoles comprising:

(a) mixing N-chlorosuccinimide and R_1SH in a liquid for sufficient temperatures and for a sufficient time to generate R_1SCl ,

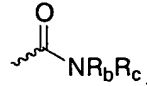


wherein R_1 is (C₁-C₆)alkyl, (C₂-C₆)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)-S(O)_mR_a, --(C₁-C₆)-S(O)_mNR_bR_c, (C₁-C₆)-NR_bR_c, or (C₁-C₆)-C(=O)-NR_bR_c, aryl, or heteroaryl, wherein (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, or (C₃-C₇)heterocycloalkyl is optionally partially unsaturated and (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, aryl, or heteroaryl, is optionally substituted with aryl, aryl(C₁-C₆)alkoxy, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, --S(O)_mR_a, --S(O)_mNR_bR_c, NR_bR_c, or --C(=O)NR_bR_c, wherein m is 1 or 2 and a, b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆)heterocycloalkyl, or aryl;

(b) combining an indole-2-carboxylate **1** with the mixture containing the sulfenyl chloride generated in step (a) to provide the sulfenylated indole **2**



wherein R_1 is as provided in step (a);

5 R_2 is carboxy, tetrazolyl, (C₂-C₆)alkoxycarbonyl, or , or --S(O)_mR_a, or --S(O)_mNR_bR_c, NR_bR_c, or COR_d, optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, or cyano, wherein R_b and R_c are each, independently H or (C₁-C₆)alkyl wherein m is 1 or 2 and a, b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆)heterocycloalkyl, or aryl; and
 10 R_3 is H or (C₁-C₆)alkyl or (C₁-C₆)alkanoyl, optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, or cyano;
 15 R_4 - R_7 are each independently H, halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)-S(O)_mR_a, --(C₁-C₆)-S(O)_mNR_bR_c, (C₁-C₆)-NR_bR_c, or (C₁-C₆)-C(=O)-NR_bR_c, (C₁-C₆)-C(=O)R₁, S(O)_mR_a, S(O)_mNR_bR_c, NR_bR_c, C(=O)-NR_bR_c, C(=O)R_d aryl or heteroaryl, wherein (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, or (C₃-C₇)heterocycloalkyl is optionally partially unsaturated and (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, aryl, or heteroaryl, is optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, --S(O)_mR_a, --S(O)_mNR_bR_c, NR_bR_c, or --C(=O)NR_bR_c, C(=O)R₁ wherein m is 1 or 2 and a, b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆) heterocycloalkyl, heteroaryl or aryl, provided that not all of R_4 - R_7 are H; and
 25

(c) mixing the mixture generated in step b for sufficient temperature and for sufficient time to generate the sulfide.

30 2. The method of claim 1, wherein R_1 in R_1SH is (C₁-C₆)alkyl, (C₂-C₆)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, aryl, or

- heteroaryl, wherein (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, or (C₃-C₇)heterocycloalkyl, or aryl is optionally partially unsaturated and (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, aryl, or heteroaryl, is optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, NR_bR_c, or --C(=O)NR_bR_c, and b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆)heterocycloalkyl, or aryl.
- 5
- 10 3. The method of claim 1, wherein R₁ in R₁SH is (C₁-C₆)alkyl or aryl, wherein (C₁-C₆)alkyl or aryl is optionally substituted with aryl, halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, NR_bR_c, or --C(=O)NR_bR_c, and b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆)heterocycloalkyl, or aryl.
- 15
4. The method of claim 1, wherein R₁ in R₁SH is (C₁-C₆)alkyl or aryl, wherein (C₁-C₆)alkyl or aryl is optionally substituted with halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, NR_bR_c, or --C(=O)NR_bR_c, and b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆)heterocycloalkyl, or aryl.
- 20
5. The method of claim 1, wherein R₁ in R₁SH is (C₁-C₆)alkyl or aryl, wherein (C₁-C₆)alkyl or aryl is optionally substituted with halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, NR_bR_c, or --C(=O)NR_bR_c, and b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, or aryl.
- 25
6. The method of claim 1, wherein contacting in step (a) comprises mixing the NCS and thiol in a liquid to form a homogeneous or heterogeneous mixture.
- 30

7. The method of claim 1, wherein the liquid in step (a) is a polar aprotic solvent selected from tetrahydrofuran, diethyl ether, acetonitrile, nitromethane, chloroform, methylene chloride, monochloro ethane, 1,1, or 1,2 dichloroethane, 1,1,1 or 1,1,2 trichloroethane, or 1,1,1,2, or 1,1,2,2 tetrachloroethane or combinations thereof.
5
8. The method of claim 1, wherein the liquid in step (a) is methylene chloride or chloroform or mixtures thereof.
- 10 9. The method of step (a) of claim 1, wherein about 1.01 to about 1.2 equivalent of NCS is used for each equivalent of thiol.
10. The method of step (a) of claim 1, wherein the concentrations of NCS and thiol are typically in the range of about 0.05 to about 0.3 M each respectively.
15
11. The method of step (a) of claim 1, wherein the concentration of NCS and thiol are typically in the range of about 0.1 to about 0.25 M each respectively.
12. The method of step (a) of claim 1, wherein concentrations of NCS and thiol are typically in the range of about 0.15 to about 0.2 M each respectively.
20
13. The method of step (a) of claim 1, wherein reaction times are in the range of about 10 minutes to about 30 minutes.
- 25 14. The method of step (a) of claim 1, wherein reaction times are in the range of 12 minutes to 20 minutes.
15. The method of step (a) of claim 1, wherein reaction times are 15 minutes.
- 30 16. The method of step (a) of claim 1, wherein the NCS and thiol are mixed in the liquid at temperatures in the range of about -90 to -25 °C.

17. The method of step (a) of claim 1, wherein wherein the NCS and thiol are mixed in the liquid at temperatures in the range of about -79 to -70 °C.
18. The method of step (b) of claim 1, wherein the indole-2-carboxylate in a solvent is added to the sulfenyl chloride generated during step (a) of claim 1.
19. The method of step (b) of claim 1, wherein the indole is added as a solution in a polar aprotic solvent as recited in claim 7.
20. The method of step (b) of claim 1, wherein the indole is added as a solution in a polar aprotic solvent is methylene chloride.
21. The method of step (b) of claim 1, wherein the concentration of the indole in the solvent is between about 0.1 to about 1.0 M.
22. The method of step (b) of claim 1, wherein the concentration of the indole in the solvent is between about 0.2 to about 0.9 M.
23. The method of step (b) of claim 1, wherein the concentration of the indole in the solvent is between about 0.3. to about 0.7 M.
24. The method of step (b) of claim 1, wherein the mixture of the indole in the solvent is added to the chilled mixture of the sulfenyl chloride at a rate sufficient to maintain the reaction temperature at below -70 °C. The completion of the addition step culminates in the formation of a mixture containing sulfenyl chloride and indole.
25. The method of step (b) of claim 1, wherein about 1.01 to about 1.5 equivalents of sulfenyl chloride are used for each equivalent of indole used.
26. The method of step (b) of claim 1, wherein about 1.05 to about 1.3 equivalents of sulfenyl chloride are used for each equivalent of indole used.

27. The method of step (b) of claim 1, wherein about 1.09 to about 1.25 equivalents of sulfenyl chloride are used for each equivalent of indole used.

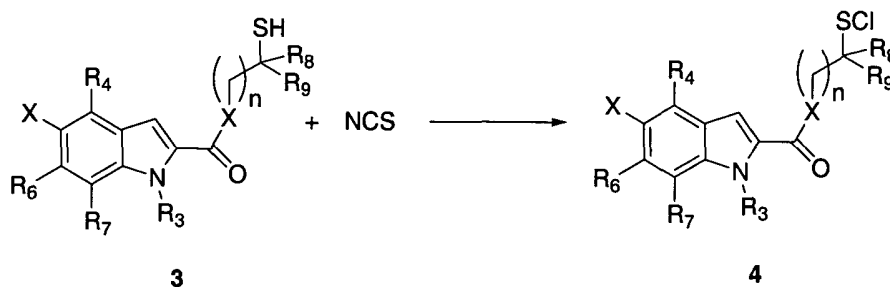
5 28. The method of step (b) of claim 1, wherein the mixture containing the sulfenyl chloride and indole is maintained at a temperature between about -79 to -70 °C for up to about 15 to 60 minutes and then is allowed to warm to about 0 °C over the course of about 1 to 2 hours.

10 29. The method of step (c) of claim 1, wherein about the solvent from step (b) of claim 1 is removed by evaporation.

30. A method for the intramolecular sulfenylation of 2-carboxyindoles comprising comprising:

15

(a) mixing N-chlorosuccinimide with compound **3** in a liquid for sufficient temperatures and for a sufficient time to generate compound **4**,



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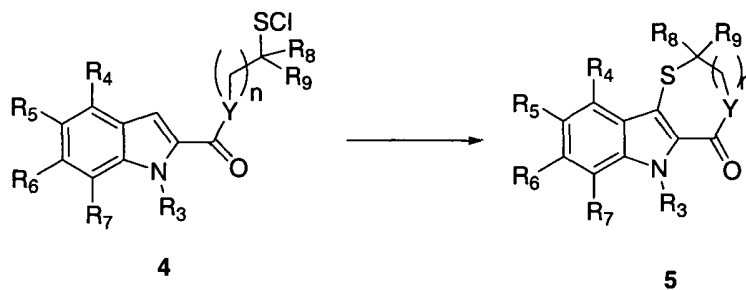
wherein R₃ is H or (C₁-C₆)alkyl or (C₁-C₆)alkanoyl, optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, or cyano;

25

R₄- R₆ and R₇ are independently H, halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, Cyano, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)-S(O)_mR_a, --(C₁-C₆)-S(O)_mNR_bR_c, (C₁-C₆)-NR_bR_c, or (C₁-C₆)-C(=O)-NR_bR_c, (C₁-C₆)-C(=O)R₁, S(O)_mR_a, S(O)_mNR_bR_c, NR_bR_c, C(=O)-NR_bR_c, C(=O) R₁ aryl or heteroaryl, wherein (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, or (C₃-C₇)heterocycloalkyl is

optionally partially unsaturated and (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)heterocycloalkyl, aryl, or heteroaryl, is optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkanoyloxy, --S(O)_mR_a, --S(O)_mNR_bR_c, NR_bR_c, or --C(=O)NR_bR_c, C(=O)R₁ wherein m is 1 or 2 and a, b, and c are each independently H, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₆) heterocycloalkyl, heteroaryl or aryl, provided that not all of R₄-R₇ are H; R₈ and R₉ are independently H or (C₁-C₆)alkyl optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, or cyano; n is 0-4; and X is CR₇R₈, O, or NR_b, wherein R_b is H, acyl, or (C₁-C₆)alkyl, optionally substituted with aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxy, nitro, halo, or cyano; and

(b) allowing the sulfenyl chloride **4** generated in step (a) to provide the sulfenylated indole **5**.



31. The method of claim 30, wherein R₃ in compounds 4-6 is H and (C₁-C₆)alkyl; R₄ and R₅ are independently H or (C₁-C₆)alkyl; n is 1, 2, or 3; and X is H, halo or (C₁-C₆)alkoxy.
32. The method of claim 31, wherein R₃ in compounds 4-6 is H or methyl;

R₄ and R₅ are independently H or methyl;

n is 1, 2, or 3; and

X is H, halo or methoxy.

- 5 33. The method of claim 30, wherein contacting in step (a) comprises mixing the
NCS and thiol in a liquid to form a homogeneous or heterogeneous mixture.
- 34 The method of claim 30, wherein the liquid in step (a) is a polar aprotic
solvent as recited in claim 7.
- 10 35. The method of claim 30, wherein the liquid in step (a) is methylene chloride or
chloroform or mixtures thereof.
- 15 36. The method of step (a) of claim 30, wherein reaction times are in the range of
about 10 minutes to about 30 minutes.
37. The method of step (a) of claim 30, wherein reaction times are in the range of
12 minutes to 20 minutes.
- 20 38. The method of step (a) of claim 30, wherein reaction times are 15 minutes.
39. The method of step (a) of claim 30, wherein the NCS and thiol-substituted
indole are mixed in the liquid at temperatures in between about -90 to -25 °C.
- 25 40. The method of step (a) of claim 30, wherein wherein the NCS and thiol-
substituted indole are mixed in the liquid at temperatures in between about -
79 to -70 °C.
- 30 41. The method of step (a) of claim 30, wherein about 1.01 to about 1.2 equivalent
of NCS is used for each equivalent of thiol-substituted indole.

42. The method of step (a) of claim 1, wherein the concentration of the thiol-substituted indole in the solvent is between about 0.1 to about 1.0 M.
- 5 43. The method of step (a) of claim 30, wherein the concentration of the thiol-substituted indole in the solvent is between about 0.2 to about 0.9 M.
44. The method of step (a) of claim 30, wherein the concentration of the thiol-substituted indole in the solvent is between about 0.3. to about 0.7 M.
- 10 45. The method of step (b) of claim 30, wherein the mixture of the thiol-substituted indole in the solvent is added to the chilled mixture of the sulfenyl chloride at a rate sufficient to maintain the reaction temperature at below -70 °C. The completion of the addition step culminates in the formation of a mixture containing sulfenyl chloride and indole.
- 15 46. The method of step (b) of claim 30, wherein about 1.01 to about 1.5 equivalents of sulfenyl chloride are used for each equivalent of thiol-substituted indole used.
- 20 47. The method of step (b) of claim 30, wherein about 1.05 to about 1.3 equivalents of sulfenyl chloride are used for each equivalent of thiol-substituted indole used.
- 25 48. The method of step (b) of claim 30, wherein about 1.09 to about 1.25 equivalents of sulfenyl chloride are used for each equivalent of thiol-substituted indole used.
- 30 49. The method of step (b) of claim 30, wherein the mixture containing the sulfenyl chloride and thiol-substituted indole is maintained at a temperature between about -79 to -70 °C for up to about 15 to 60 minutes and then is allowed to warm to about 0 °C over the course of about 1 to 2 hours.

50. The method of step (c) of claim 30, wherein the solvent from step (b) of claim 30 is removed by evaporation.